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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/750,118 | 12/31/2003 | Peter Sterling Mueller | 893-2 CIP II /DIV | 9765 |

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| EXAMINER | |
|---|---|
| ROYDS, LESLIE A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1614 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/750,118 | MUELLER, PETER STERLING | |
| | Examiner | Art Unit | |
| | Leslie A. Royds | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,3,5-7,10,11,18,19,22,23,26-28 and 31-41* is/are pending in the application.

4a) Of the above claim(s) *1,3,5-7,10,11,18,19,22,23,26-28,31-34 and 39-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**Claims 1, 3, 5-7, 10-11, 18-19, 22-23, 26-28 and 31-41 are presented for examination.**

**Applicant is notified that the finality of the previous Office Action dated July 6, 2007 is hereby withdrawn. The after-final amendment filed August 27, 2007 has been entered into the record and prosecution of the present application has been reopened.**

Applicant's after-final amendment filed August 27, 2007 has been received and entered into the instant application. Claims 1, 3, 5-7, 10-11, 18-19, 22-23, 26-28 and 31-41 are pending. Claims 1, 3, 5-7, 10-11, 18-19, 22-23, 26-28, 31-34 and 39-41 remain withdrawn from consideration pursuant to 37 C.F.R. 1.142(b) and claims 35-38 are under examination. Claim 35 is amended.

Applicant's arguments and amendments, filed August 27, 2007, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

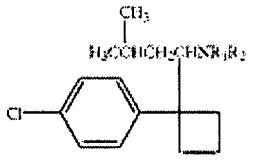
### *Claim Rejections - 35 USC § 102 (New Grounds of Rejection)*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 35 and 37 are rejected under 35 U.S.C. 102(e) as being anticipated by Mendel et al. (U.S. Patent No. 6,376,553; Published April 2002, Filed March 2000) in light of Stanton-Hicks et al. ("Reflex Sympathetic Dystrophy: Changing Concepts and Taxonomy", *Pain*, 1995, 63:127-133), cited to show a fact.

In accordance with MPEP §2131.01, it is proper to rely upon a secondary reference for a rejection under 35 U.S.C. 102, provided that the additional reference is relied upon to demonstrate that a characteristic not disclosed in the primary reference is, in fact, inherent.

Mendel et al. discloses compounds of formula I, defined as  (col.1, l.12-23), for use in a method for treating pain by administration of a therapeutically effective amount of a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof (col.1, l.9-26). Mendel et al. teaches that compounds of formula I, wherein R1=CH3 and R2=CH3, is synonymous with sibutramine (col.4, l.52-54), and further discloses the use of pharmaceutically acceptable salts of the compounds of formula I (col.1, l.12-23). Mendel et al. teaches an effective dose of the disclosed compound(s) in the range of 0.1-50 mg, preferably 1-30 mg per day (col.2, l.54-63) and further teaches that the compounds may be formulated into tablets in a manner so as to provide sustained release of the compound (col.3, l.1-13).

Though it is noted that Mendel et al. does not explicitly teach the treatment of a subject with reflex sympathetic dystrophy or complex regional pain syndrome, Applicant is advised that the instant claims are not expressly drawn to the treatment of a subject suffering from reflex sympathetic dystrophy or complex regional pain syndrome, but rather to a human in need of treatment of the "symptoms of reflex sympathetic dystrophy or complex regional pain syndrome". Please see, e.g., claim 35. In view of the manner in which the claim is written, the prior art of Mendel et al. meets the claimed subject in whom the instant method is practiced because the present claims solely require that the patient be suffering from a *symptom* of reflex sympathetic dystrophy or complex regional pain syndrome, of which pain is very obviously a symptom, as evidenced by Stanton-Hicks et al. (see, e.g., abstract at page 127). Accordingly, the very teaching of sibutramine for the treatment of pain clearly meets the instantly claimed method

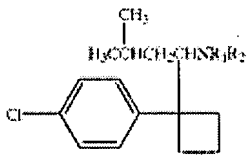
directed to the treatment of a *symptom* (i.e., pain) of reflex sympathetic dystrophy or complex regional pain syndrome by administering a pharmaceutically effective amount of sibutramine (or a pharmaceutically acceptable salt thereof) for treating said *symptom* in a human in need thereof.

***Claim Rejections - 35 USC § 103 (New Grounds of Rejection)***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mendel et al. (U.S. Patent No. 6,376,553; Published April 2002, Filed March 2000) in light of Stanton-Hicks et al. ("Reflex Sympathetic Dystrophy: Changing Concepts and Taxonomy", *Pain*, 1995, 63:127-133) in view of Huff et al. (U.S. Patent No. 4,302,455; 1981).

Mendel et al. discloses compounds of formula I, defined as  (col.1, l.12-23), for use in a method for treating pain by administration of a therapeutically effective amount of a compound of formula I in conjunction with a pharmaceutically acceptable diluent or carrier to a human in need thereof (col.1, l.9-26). Mendel et al. teaches that compounds of formula I, wherein R1=CH3 and R2=CH3, is synonymous with sibutramine (col.4, l.52-54), and further discloses the use of pharmaceutically acceptable salts of the compounds of formula I (col.1, l.12-23). Mendel et al. teaches an effective dose of the disclosed compound(s) in the range of 0.1-50 mg, preferably 1-30 mg per day (col.2, l.54-63) and further teaches that the compounds may be formulated into tablets in a manner so as to provide sustained release of the compound (col.3, l.1-13).

Though it is noted that Mendel et al. does not explicitly teach the treatment of a subject with reflex sympathetic dystrophy or complex regional pain syndrome, Applicant is advised that the instant claims are not expressly drawn to the treatment of a subject suffering from reflex sympathetic dystrophy or complex regional pain syndrome, but rather to a human in need of treatment of the "symptoms of reflex sympathetic dystrophy or complex regional pain syndrome". Please see, e.g., claim 35. In view of the manner in which the claim is written, the prior art of Mendel et al. meets the claimed subject in whom the instant method is practiced because the present claims solely require that the patient be suffering from a *symptom* of reflex sympathetic dystrophy or complex regional pain syndrome, of which pain is very obviously a symptom, as evidenced by Stanton-Hicks et al. (see, e.g., abstract at page 127). Accordingly, the very teaching of sibutramine for the treatment of pain clearly meets the instantly claimed method directed to the treatment of a *symptom* (i.e., pain) of reflex sympathetic dystrophy or complex regional pain syndrome by administering a pharmaceutically effective amount of sibutramine (or a pharmaceutically acceptable salt thereof) for treating said *symptom* in a human in need thereof.

The differences between the primary reference to Mendel et al. and the instantly claimed subject matter lie in that the reference does not explicitly teach a dosage amount of sibutramine (or salt thereof) in the range of about 0.25 mg-45 mg per day (claim 36) or the concomitant use of an antiepileptic or antidepressant medication (claim 38).

Regarding the instantly claimed dosage amount (i.e., about 0.25 mg-about 45 mg/day, claim 36), Mendel et al. expressly teaches the use of a dosage amount of from 0.1-50 mg/day, preferably 1-30 mg/day, which encompasses Applicant's instantly claimed narrower range of 0.25-45 mg/day. As taught by MPEP §2144.05(I) with regard to the obviousness of ranges, "[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a *prima facie* case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). In accordance with this teaching, Mendel et al. renders the instantly claimed dosage amount of sibutramine

(or a salt thereof) *prima facie* obvious, absent factual evidence to the contrary.

Even if, for the sake of argument, such ranges were not necessarily *prima facie* obvious from the prior art teaching of 0.1-50 mg/day in Mendel et al., Mendel et al. expressly teaches that, "The amount of the compound to be administered will depend on a number of factors, including the age of the patient, the severity of the condition and the past medical history of the patient and always lies within the sound discretion of the administering physician but it is generally envisaged that the dosage of the compound to be administered will be in the range 0.1 to 50 mg preferably 1 to 30 mg per day given in one or more doses." Please see col.2, l.54-63.

It is obvious from the above teachings that Mendel et al. expressly contemplates variation in the dosage amount of the active agent and specifically acknowledges that such a matter was well within the skill of the artisan at the time of the invention and would not have required undue experimentation or have been outside the realm of knowledge generally available to the skilled artisan. Factors that would also have been taken into consideration when making such a determination would have included, but not been limited to, the weight, sex, diet and medical condition of the patient, route of administration, pharmacological considerations, e.g., activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen that would have actually been employed would have been expected to vary widely and, in the absence of evidence to the contrary, would not have been inconsistent with that which is presently claimed.

In addition, the concentration of the active ingredient is a result-effective variable, i.e., a variable that achieves a recognized result, and, therefore, the determination of the optimum of workable dosage range would be well within the practice of routine experimentation by the skilled artisan, absent factual evidence to the contrary, and, further, absent any evidence demonstrating a patentable difference between the compositions used and the criticality of the amount(s).

Huff et al. is cited for its teachings of 2-(4-aminopiperidino)pyrazine compounds effective as analgesic and antidepressant agents, due to their serotoninergic properties (abstract, col.1, l.20-23).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine the sibutramine of Mendel et al. with the analgesic and antidepressive 2-(4-aminopiperidino)pyrazine compounds of Huff et al. because both the sibutramine of Mendel et al. and the antidepressant 2-(4-aminopiperidino)pyrazine compounds of Huff et al. were each known in the art to have the same efficacy in the treatment of pain. Motivation to make such a combination flows logically from the very fact that each was known in the prior art to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two compounds, when combined, would have, at minimum, additive, if not synergistic, effects when combined.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

***Conclusion***

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference U.S. Patent No. 6,331,571 to Jerussi et al. ("Methods of Treating and Preventing Attention Deficit Disorders").

Rejection of claims 35-38 remains proper and is **maintained**.

Claims 1, 3, 5-7, 10-11, 18-19, 22-23, 26-28, 31-34 and 39-41 remain **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leslie A. Royds
Patent Examiner
Art Unit 1614

September 27, 2007

9/28/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER